The Examiner has acknowledged Applicants' election with traverse of group I, claims 1-8 and 80-84. Furthermore, the Office Action has apparently continued to treat as legitimate and final the illegitimate action of invading the structure of several of the claims to remove *en masse* the larger part of the claimed invention by insisting that all but one of the sequences of various primers (SEQ ID Nos. 1-18) must be removed before a search can be conducted. Applicants know of no authority for such a practice and respectfully request that Examiner provide such support. Furthermore, Applicants note that, with all due respect, the Office Action provides no authority supporting the procedural legitimacy of a demand that Applicants either "state on the record that each of the claimed nucleic acid sequences of SEQ ID Nos. 1-18 were well known in the art at the time the invention was made," or be subject to be subject to an improper and draconian restriction requirement. The Office Action appears to attempt to draw upon the paucity of case law concerning restriction practice when it calls upon Applicants to cite legal authority against an improper procedural action which has been taken without legal support from the patent statutes, patent rules or any other procedural authority (i.e the MPEP).

Applicants hereby respectfully preserve this issue for appeal and will treat any limitation of the claims to a single primer/ SEQ ID NO. as a species election requirement. Indeed, Applicants note that the only legitimate such restriction occurs for search purposes only as a part of species election in the chemical arts. This practice differs significantly from restriction practice, inasmuch as an elected species, if found allowable, entitles the Applicant to a further search of the remaining previously unelected species.

Objection to the Specification

The Office Action states that, "if applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application." Accordingly, Applicants have amended their priority claim to indicate that the present invention "is a continuation-in-part of International Application PCT/US99/08794, filed April 21, 1999."

REJECTIONS

Rejection Under 35 U.S.C. §112, first paragraph- Enablement

The Office Action states that claims 1-8 and 80-84 are rejected under 35 U.S.C. § 112, first paragraph as not enabling the skilled artisan to practice the claimed invention. In particular, the Office Action states that "the specification, while being enabling for methods for determining a pregnant woman's predisposition to having a low birth weight baby comprising detecting the presence of IL-1A (+4845) allele 2 or IL-1B (-511) allele 2....does not reasonably provide enablement for methods which determine a predisposition to any adverse pregnancy outcome by detecting (an) allele in linkage disequilibrium (to these alleles)." Applicants respectfully traverse this rejection to the extent that it is maintained over the claims as amended in this action. In particular, Applicants have provided the skilled artisan with extensive support and guidance regarding the claimed methods of use of an IL-1A (+4845) allele 2 and an IL-1B (-511) allele 2 as well as the corresponding alleles found in linkage disequilibrium with these alleles in the 33221461 and 44112332 haplotypes respectively. Applicants have amended the instant claims in order to clarify that the claimed invention is extensive with the scope supported by these teachings. It is Applicants' belief that these clarifying amendments obviate the instant rejection under 35 U.S.C. § 112 for lack of enablement, and, accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Notwithstanding Applicants' belief that the instant amendments obviate the rejection for lack of enablement made in the Office Action dated April 4, 2002, Applicants note further for the record that this rejection is improperly maintained. In particular, Applicants respectfully note that, notwithstanding assertions to the contrary, examples included in the specification do not generally limit what is covered by the claims (see MPEP § 2164.08). In particular, the Office Action states that enablement in the instant application extends only to the working examples cited by the Examiner (i.e. "The specification (page 63) teaches that "White women showed a trend towards association between individuals carrying at least 1 copy of allele 2 at +4845 and -511 and low birth weight...Accordingly the specification teaches"). Applicants respectfully note that enablement of the claimed invention is not necessarily limited to any one particular

working example disclosed in the specification. In particular, MPEP § 2164.08 states that "How a teaching is set forth, by specific example or broad terminology, is not important. In re Marzocchi, 439 F.2d 220, 223-24 169 USPQ 367 , 370 (CCPA 1971)." Furthermore, Applicants respectfully note that enablement commensurate in scope with the claims is determined under a standard of "reasonable correlation" (see MPEP § 2164.08 summarizing *In re Fisher* 427 F.2d 833, 839) and that such reasonable correlation standard is met in this instance.

Rejection Under 35 U.S.C. §112, second paragraph- Indefiniteness

The Office Action states that claims 1-8 and 8-84 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action states that "claims 1-8 are indefinite and vague over the recitation of IL-1(-511) because the claims do not set forth the complete identity of the stated allele.....the claims should be amended to refer to 'IL-1B(-511).'" Accordingly, Applicants have amended claims 1 and 8 to reflect the IL-1B (-511) allele, and so reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action states that claims 1-8 are indefinite for the recitation of "the fetus" without proper antecedent basis. Accordingly, claim 1 has been amended to reflect the predisposition of the subject (which has antecedent support) to an adverse pregnancy outcome and so reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action states that claim 8 is indefinite for failing to recite a final process step which reflects the purpose presented in the preamble. Accordingly, Applicants have amended claim 8 to reflect the claimed subject matter of a method of identifying an allele associated with low birth weight, and so reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action states that claims 80-82 are indefinite for the recitation of "the individual's increased susceptibility to adverse pregnancy outcome" without complete and proper antecedent support. Accordingly, Applicants have amended claim 80 to reflect the claimed subject matter of a method of predicting an adverse pregnancy

outcome in an individual by obtaining a specimen from a fetus from the individual. Therefore reconsideration and withdrawal of the rejection is respectfully requested.

The Office Action states that claims 83-84 are indefinite and vague for the recitation of "similarity" and "IL-1A allele 2." Accordingly, Applicants have amended claim 83 to reflect the claimed subject matter of a method of predicting an increased susceptibility to adverse pregnancy "wherein the presence of the IL-1A(+4845) and the IL-1B(Taq I) allele 2 in the genetic polymorphism pattern in the genomic DNA indicates susceptibility to an adverse pregnancy outcome." Furthermore, Applicants have also amended claim 83 to reflect the detection of an IL-1A(+4845) allele 2. Therefore reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting

Finally, the Office Action states that claims 1-8 and 80-84 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,268,142. In particular, the Office Action states that "although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims and the claims of '142 are both inclusive of methods for diagnosing a disease by detecting the presence of IL-1A(+4845) allele 2 or IL-1B (-511) allele 2." Applicants respectfully request that this rejection be held in abeyance until such time as a finding of allowable subject matter in the instant application is made. At that time, Applicants will prepare and file a terminal disclaimer of the instant application to the '142 patent if the allowable subject matter so merits.

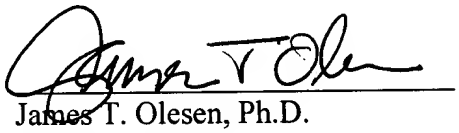
CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance, and early notification of such is respectfully requested. If for any reason a telephonic conference with the Applicant would be helpful in expediting

prosecution of the instant application, the Examiner is invited to call Applicants' Attorney at (617) 832-1000.

If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. **06-1448**.

Respectfully submitted,

By: 
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Dated: October 4, 2002

Marked-up version of the claims in 09/693,555 pending and under consideration, showing changes made

1. **(Amended)** A method for determining whether a subject is predisposed to having an adverse pregnancy outcome, said method comprising the steps of:

a) obtaining a nucleic acid sample from the subject; and

b) detecting an IL-1A (+4845) allele 2 or an IL-1B (-511) allele 2 or an allele of the 33221461 haplotype in linkage disequilibrium with an IL-1A (+4845) allele 2 or an allele of the 44112332 haplotype in linkage disequilibrium with an IL-1B (-511) allele 2 in a sample, wherein detection of [the IL-1A (+4845) allele 2 or the IL-1B (-511) allele 2 or the allele in linkage disequilibrium with the IL-1A (+4845) allele 2 or the IL-1B (-511) allele 2] said allele indicates that the [fetus] subject is predisposed to an adverse pregnancy outcome.

2. The method of claim 1, wherein the adverse pregnancy outcome is low birth weight.

3. The method of claim 1, wherein said detecting step is selected from the group consisting of allele specific oligonucleotide hybridization; size analysis; sequencing; hybridization; 5'nuclease digestion; single-stranded conformation polymorphism; allele specific hybridization; primer specific extension; and oligonucleotide ligation assay.

4. The method of claim 1, wherein prior to the detection step, the nucleic acid sample is subject to an amplification step.

5. The method of claim 4, wherein said amplification step employs a primer selected from the group consisting of any of SEQ ID No: 1 through SEQ ID No:18.

6. The method of claim 3, wherein said size analysis is preceded by a restriction enzyme digestion.

7. A method of claim 6, wherein said restriction enzyme digestion uses a restriction enzyme selected from the group consisting of: Nco I, Alu I and Msp I.

8. **(Amended)** A method of identifying an allele associated with [an] low birth weight, said method comprising identifying an allele in the 33221461 haplotype [, which] that is in linkage disequilibrium with IL-1A (+4845) allele 2 and/or an allele in the 44112332 haplotype that is in linkage disequilibrium with IL-1B (-511) allele 2 , thereby identifying an allele associated with low birth weight.

80. **(Amended)** A method of determining increased susceptibility to an adverse pregnancy outcome in an individual, said method comprising:

[(a)] detecting [an IL-1 allele 2 of a marker] in a nucleic acid from a specimen collected from a fetus from the individual an IL-1 allele selected from the group consisting of: an IL-1A (+4845) allele 2, an allele of the 33221461 haplotype in

linkage disequilibrium with an Il-1A (+4845) allele 2, an IL-1B (-511) allele 2, and an allele of the 44112332 haplotype in linkage disequilibrium with an Il-1B (-511) allele 2;

wherein detecting said IL-1 allele [2 marker] indicates the individual's increased susceptibility to an adverse pregnancy outcome.

81. The method of claim 80, wherein said adverse pregnancy outcome is a premature preterm-low birth weight delivery.

82. The method of claim 80, wherein said detecting comprises PCR amplification of the DNA using a primer that overlaps with an oligonucleotide selected from the group consisting of: SEQ. ID. Nos: 1-18.

83. **(Amended)** A method of predicting increased susceptibility to adverse pregnancy outcome comprising:

determining a genetic polymorphism pattern in genomic DNA for IL-1A and IL-1B and comparing the pattern to a control sample, wherein the control sample comprises an IL-1A(+4845) allele 2 and an IL-1B (Taq I) allele 2; and wherein the [similarity of the] presence of the IL-1A(+4845) and the IL-1B(Taq I) allele 2 in the genetic polymorphism pattern in the genomic DNA [to the control sample] indicates susceptibility to an adverse pregnancy outcome.

84. The method of claim 83, wherein said step for determining a genetic polymorphism pattern comprises amplification with a PCR primer selected from the group consisting of:

5' TGT TCT ACC ACC TGA ACT AGG C 3' (SEQ ID No: 1);

5' TTA CAT ATG AGC CTT CCA TG 3' (SEQ ID No: 2);

5' TGG CAT TGA TCT GGT TCA TC 3' (SEQ ID No: 3);

5' GTT TAG GAA TCT TCC CAC TT 3' (SEQ ID No: 4);

5' CTC AGG TGT CCT CGA AGA AAT CAA A 3' (SEQ ID No: 5);

5' GCT TTT TTG CTG TGA GTC CCG 3' (SEQ ID No: 6).

5' ATGGTTTTAGAAATCATCAAGCCTAGGGCA 3' (SEQ ID No: 7)

5' AATGAAAGGAGGGGAGGATGACAGAAATGT 3' (SEQ ID No: 8)

5' CTATCTGAGGAACAACCAACTAGTAGC 3' (SEQ ID No: 9)

5' TAGGACATTGCACCTAGGGTTTGT 3' (SEQ ID No: 10)

5' AGGCAATAGGTTTTGAGGGCCAT 3' (SEQ ID No: 11)

5' TCCTCCCTGCTCCGATTCCG 3' (SEQ ID No: 12)

5' GAAGCCCCTCCCAGTTCTAGTTC 3' (SEQ ID No: 13)

5' CACTCCCCATCCTCCCTGGTC 3' (SEQ ID No: 14)

5' CTCAGCAACACTCCTAT 3' (SEQ ID No: 15)

5' TCCTGGTCTGCAGGTAA 3' (SEQ ID No: 16)

5' AAGCTTGTTCTACCACCTGAACTAGGC 3' (SEQ ID No: 17)

5' TTACATATGAGCCTTCCATG 3' (SEQ ID No: 18)

Marked-up version of the specification in 09/693,555, showing changes made

Please replace the first paragraph on page 1 with the following paragraph:

Priority Information and Incorporation by Reference

The present application [claims benefit of priority to] is a continuation-in-part of International Application Number PCT/US99/08794, filed April 21, 1999, which claims priority to U.S. Provisional Application Number 60/082,487, filed April 21, 1998. The contents of both of these priority applications are incorporated herein by reference in their entirety. This application hereby further incorporates by reference in its entirety the contents of Applicant's copending application 09/345,217 filed on June 30, 1999, which issued as U.S. Patent No. 6,268,142 on July 31, 2001.